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GUIDELINES FOR CONDUCT AND REPORTING OF GOOD CLINICAL PRACTICE INSPECTIONS

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This draft guideline is uploaded on the official website of DRAP on 22nd February 2024 for seeking comments and suggestions from stakeholders on the draft document. Stakeholders can submit their comments and suggestions within 15 days of uploading this document using prescribed format, (further information on comments submission can access on this link. Comments and suggestions can be forwarded via email to shafqat.hussain@dra.gov.pk with copy to dir.ps@dra.gov.pk or can be posted at following mailing address: Assistant Director (Clinical Research), Pharmacy Services Division, Drug Regulatory Authority of Pakistan, DRAP-NCLB Building, Prime Minister's Health Complex, Park Road, Chak Shahzad, Islamabad, Pakistan.

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Drug Regulatory Authority of Pakistan
Islamabad-Pakistan

1. HISTORY

This is the second edition of this document.

2. APPLICATION

These guidelines are applicable to the Sponsors, Principal Investigators (PI), Site Investigators (SI), Contract Research Organizations (CROs), Clinical Trial Site, BA/BE Study Center and Bio-Analytical Laboratories involved in conduct of Clinical Research related to therapeutic goods and to the CSC nominated experts / Clinical Research applications Evaluators/Assessors / GCP inspectorate of the DRAP to explain the procedure conduct and reporting of GCP inspections of Clinical Research related to therapeutic goods regulated by the DRAP.

3. PURPOSE

This document is intended to provide general guidance to applicants (e.g. the Sponsors, Principal Investigators, Site Investigators, Contract Research Organization (CROs), Clinical Trial Site, BA/BE Study Center and Bio-Analytical Laboratories) involved in conduct of Clinical Research related to therapeutic goods and guideline describes the regulatory requirements and procedure for conduct and reporting of GCP inspections to the CSC nominated experts / Clinical Research applications Evaluators/Assessors / GCP inspectors of the DRAP involved in Clinical Research Oversight activities.

DRAFT FOR COMMENTS

Table of Contents

DRAFT FOR COMMENTS

4. GLOSSARY (ABBREVIATIONS / ACRONYMS)

ADR	Adverse Drug Reaction
ALSS	Advanced Life Support Systems
BA/BE	Bioavailability / Bioequivalence
BAL	Bioanalytical Laboratory
CoA	Certificate of Analysis
CPR	Cardio-pulmonary resuscitation
CR	Clinical Research (pertains to Clinical Trial or BA/BE Study)
CRO	Contract Research Organization
CRF	Case Report Form
CSC	Clinical Studies Committee
CV	Curriculum Vitae
DRAP	Drug Regulatory Authority of Pakistan
DSMB	Data Safety Monitoring Board
ERC	Ethics Review Committee
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRC	Institutional Review Committee
ISF	Investigator's Site File
NA	Not applicable
NBC	National Bio-Ethics Committee
PI	Principal Investigator
SI	Site Investigator
RA	Regulatory Authority
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
WHO	World Health Organization

DRAFT FOR COMMENTS

5. Definitions:

Adverse Drug Reaction	"Adverse drug reaction" or "ADR" means response to medicines which is noxious and unintended that occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease or for the restoration, correction or modification of physiological function. A response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected; ***OR*** In the pre-approval clinical experience with a new therapeutic goods or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.
Adverse Event	"Adverse event" or "AE" means any untoward medical occurrence in a patient or clinical investigation subject administered a medicine and which does not necessarily have a causal relationship with this treatment; OR Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
Applicable Regulatory Requirement(s)	DRAP Act, 2012 Bio-Study Rules, 2017 DRAP's Guidelines on Conduct of Clinical Research in Pakistan Latest ICH-GCP Guidelines.
Audit	A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and other applicable regulatory requirement(s).
Audit Certificate	A declaration of confirmation by the auditor that an audit has taken place.
Audit Report	A written evaluation by the Sponsor's or Regulatory Authority's auditor of the results of the audit.
Audit Trail	Documentation that allows reconstruction of the course of Audit.
Blinding/Masking	A procedure in which one or more parties to the trial are kept unaware of the treatment/intervention assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment/intervention assignment(s).
Case Report Form (CRF)	A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.
Clinical Research	Any type of research involving Human Subjects with Clinical Intervention of therapeutic goods. e.g. Clinical Trial(s) and/or BA/BE Study.
Clinical Trial / Research Application	The Clinical Trial/Research application is the dossier that includes all documentation pertaining to the conduct of clinical trial/research in country according to the regulation. The dossier includes a cover letter, CV's of investigators, protocol and an investigator's brochure or product information etc. (Protocol and Investigator's brochure should be in accordance with ICH- GCP guidelines).
IMPs/Drug Import License (DIL)	DRAP, authorizing the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered / enlisted product, or a license issued by DRAP authorizing the licensee to import any registered / enlisted or unregistered /un-enlisted product for purposes of clinical trials.

DRAFT FOR COMMENTS

Clinical Trial/ Study Report	A written description of a trial/study of any investigational product conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).
Clinical Trial/Study	Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other Pharmacodynamics effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.
Clinical Trials (Phase)	A systematic study on therapeutic goods products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety. Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist.
Clinical Trial / Study Report	A written description of a trial/study of any investigational product conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into asingle report
Comparator Product	An investigational or marketed product (i.e. active control) or placebo, used as a reference in a Clinical Trial.
Compliance (in relation to trials)	Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.
Confidentiality	Prevention of disclosure, to other than authorized individuals, of a Sponsor's proprietary information or of a subject's identity.
Contract	A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.
Contract Research Organization (CRO)	A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial- related duties and functions.
Co-Investigator / Sub investigator	Any individual member of the clinical trial team designated and supervised by the Principal Investigator at a trial site to perform critical trial- related procedures and/or to make important trial-related decisions, (e.g., associates, residents, research fellows).
Direct Access	Permission to examine, analyze, verify, and reproduce any records and reports that are important for evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.
Documentation	All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms etc.) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.
Drug Regulatory Authority of Pakistan (DRAP)	National Regulatory Authority established in Pakistan for the purpose of regulating the Control of Therapeutic Goods. Regulates all activities related to import, procurement of raw and packing materials, production and import of finished therapeutic goods, export, sales, pricing, etc.
Essential Documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. (See Section 12 of these guidelines)
Good Clinical Practice (GCP)	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance, that the data and reported results are credible and accurate, and the rights, integrity, and confidentiality of trial subjects are protected.
Impartial Witness	A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.
Informed Consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written,

DRAFT FOR COMMENTS

	signed, and dated informed consent form. Informed consent should be in accordance with Section 4.8 of the ICH-GCP Guidelines, and should be in English, National (Urdu) and / or Local language (if required).
Inspection	The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical research/trial that may be located at the site of the trial, at the sponsor's and/or Contract Research Organizations (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).
Inspectee	One who undergoes an inspection. For these guidelines inspectee means PI, Sponsor, or Site representative involved in Clinical Research.
Institution (Medical)	Any public or private entity or agency or medical or dental facility where clinical trials are conducted.
Institutional Review Committee (IRC) or Institutional Review Board (IRB)	An independent body constituted of medical, scientific, and non- scientific members whose responsibility is to ensure the protection of the rights, safety and well–being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects and providing continuing review of trial protocol and amendments and of the methods and material to be used.
Interim Clinical Trial/ Study Report	A report of intermediate results and their evaluation based on analyses performed during the course of a trial.
Investigational Products (IPs)	A pharmaceutical dosage form of an active ingredient or placebo or any device being tested or used as a reference in a clinical trial, including a registered / enlisted product when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication or when used to gain further information about an approved use.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. Principle Investigator will be responsible for whole Clinical Studies / Trial.
Site Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team at the site and may be called the site investigator.
Investigator's Brochure	A compilation of the available clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects or animals. Investigator brochure should be in accordance with Section 7 of ICH-GCP guidelines, as per Rule 15 of the Bio-Study Rules 2017.
Manufacture	All operations that include purchase of materials and products production, quality control, release of finished products, and related controls.
Manufacturer	A company that carries out at least one step of production as well as the final release of the finished product.
Monitoring	The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), the Bio-Study Rules 2017, DRAP Act 2012 and the rules made under.
Monitoring Plan	A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.
Monitoring Report	A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.
Multi-Center Trial	A clinical trial conducted according to a single protocol but at more than one site(s) in a country, and therefore, carried out by more than one investigator.
Multi-Countries Clinical Trial	A clinical trial conducted according to a single protocol at multiple sites, situated in multiple countries.
Multi-Regional Clinical Trial	A clinical trial conducted according to a single protocol and/or with some amended protocol due to different ethnic factors of different demographic regions of the world, at multiple sites, situated in different demographic regions of the world.
Phase I	These are the first trials of a new active ingredient or new formulation in humans/animals often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of the safety and the pharmacokinetic, and where possible the pharmacodynamics profile of the active ingredient(s) in humans/animals
Phase II	These trials are performed in a limited number of subjects and are often, at a later stage, of a

DRAFT FOR COMMENTS

	comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.
Phase III	Trials in larger (and possibly varied) patient groups with the purpose of determining the short- and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.
Phase IV	Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standard as applied in premarketing studies. After a product has been placed on market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout these Guideline the term protocol refers to protocol and protocol amendments. The protocol should be in accordance with section 6 of the ICH-GCP guidelines.
Protocol Amendment	A written description of a change(s) to or formal clarification of a clinical trial protocol.
Quality Assurance (QA)	All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported incompliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).
Quality Control (QC)	The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial- related activities have been fulfilled.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
Registered / Enlisted Product	Any product approved or permitted to be marketed in the country by DRAP
Serious Adverse Event or Serious Adverse Drug Reaction	Any untoward medical occurrence that at any dose: - Results in death. - Is life –threatening. - Requires inpatient hospitalization or prolongation of existing hospitalization - Results in persistent or significant disability/in capacity, or - Results in a congenital anomaly/birth defect.
Side effect	Unintended effect occurring at normal dose related to the pharmacological properties of a drug.
Source Documents / Data	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
Subject / Participants Identification Code	A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.
Subject / Trial Subject / Participant	In this guideline, subject means human participants in a clinical Trial/BA/BE Studies. An individual who participates in a Clinical Trial/ BA/BE Studies, either as a recipient of the investigational product(s) or as a control.

DRAFT FOR COMMENTS

Trial Site	The location(s) where trial-related activities are actually conducted.
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure)
Unregistered / Un-enlisted Product	Any product that is not registered / enlisted or permitted to be marketed in the country by the DRAP.
Well-being (of the trial subjects)	The physical and mental integrity of the subjects in a Clinical Trial/ BA/BE Studies.

6. Description and Grading of GCP Inspection Finding/Observations:

Critical (CR)	• Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrityof data. • Critical observations are considered totally unacceptable.
Major (MA)	• Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrityof data. • Major observations are serious deficienciesand are direct violations of GCP principles.
Minor (MI)	• Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data.

DRAFT FOR COMMENTS

7. INTRODUCTION: -

These guidelines have been drafted in conformity with the legal requirements of the Bio-Study Rules, 2017. It is required that all the Therapeutic Goods and Health Products used in Pakistan are registered / enlisted with the Drug Regulatory Authority of Pakistan (DRAP) and any Clinical Trial using any registered / enlisted or unregistered / un-enlisted products must receive written approval (i.e. license for Clinical Trial Site and Registration for Clinical Studies) from DRAP, under the Bio-Study Rules 2017 for this purpose.

Pursuant to the Bio-Study Rules 2017, the Authority shall monitor and inspect Clinical Research Sites/Centers during the course of the research/trial and at such intervals as it may determine, this guideline has been developed to facilitate the enforcement of best practices in the conduct of approved clinical research/trials in Pakistan and, to set out the procedures that should be followed by the inspectee and the inspectorate for conduct of GCP inspection of Clinical Research in Pakistan at any stage.

As defined by the ICH-GCP, an inspection is the act by a regulatory authority of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority to be related to the clinical research/trial and that may be located at the trial site/center, at the sponsors and/or Clinical Research's facilities, or at other establishments deemed appropriate by the regulatory authority.

Good Clinical Practice (GCP) inspection is necessary to ensure the protection of the rights, safety and wellbeing of study subjects and to assure the integrity of study data. It helps to determine whether the Clinical Research is conducted in accordance with approved protocol, GCP guidelines, ethical standards and other applicable regulatory requirements. The areas for the inspection, include but are not limited to, data and information relating to regulatory approvals, ethics review committee & NBC approvals, protocols, Case Report Forms, Progress Report, Clinical Trial Reports, research participants and participant's data, Sponsors, Investigators and personnel involved in the research/trial, and laboratory data.

All clinical trials including bioavailability and bioequivalence studies, be designed, conducted, recorded and reported in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with latest ICH-GCP and the applicable regulatory requirements mentioned in the Bio-Study Rules 2017 and guidelines made under.

8. RISK BASED SELECTION OF TRIAL / RESEARCH FOR GCP INSPECTION:

The selection of trials/research for GCP inspection includes, but is not limited to the following criteria;

i. Nature of intervention or IMPs.
ii. Chances of inclusion of vulnerable populations in the trial/research.
iii. For multi-centre studies, sites with more participants will be prioritized.
iv. Studies categorized as high risk by the CSC-DRAP.
v. For multi-centre studies, sites that report more deviations and ADRs will be prioritized.
vi. Trial sites for which a complaint on the conduct of the study has been reported to CSC-DRAP.
vii. CSC deems it necessary to conduct GCP Inspection due to any reason.

9. OBJECTIVES OF GCP INSPECTIONS

The DRAP may conduct GCP inspections under the following circumstances:

i. To verify the accuracy and reliability of conduct of clinical trial/research and its data that has been submitted tosupport registration of the medicine for its Market Authorization.;
ii. To investigate a complaint about the conduct of the study at a particular site;

DRAFT FOR COMMENTS

iii. Before/upon termination of the clinical site/Clinical research;
iv. During ongoing clinical trials/research to provide real-time assessment of the investigator's conduct of the trial/research and protection of human subjects;
v. Monitoring serious adverse events notification reporting frequency;
vi. Monitoring on safety handling of investigational medicinal products and other related items;
vii. On request by the investigator/sponsor.
viii. Upon direction of the CSC or the Authority

10. NATURE OF GCP INSPECTIONS:

GCP inspections may be protocol specific inspections or system specific inspections.

10.1. Protocol specific inspections: This type of inspection will seek to ascertain whether the trial/research protocol meets the standards of GCP e.g. to determine whether the dossier data submitted to regulatory authority are credible and accurate etc.

10.2. System specific inspections: Clinical trial/research systems that may be inspected include informed consent, process of obtaining the consent, handling of investigational medicinal product, biological samples, pharmacovigilance and monitoring etc.

An inspection may be conducted at an investigator site (trial site) which is already approved by DRAP, any laboratory used for clinical trial/research analyses and facility of the Sponsor, Contract Research Organizations/facilities, acting under arrangements with a Sponsor or investigator to perform some or all of the functions of the Sponsor, may also subject to inspection.

Clinical Trial/Research Sites/Centers may be inspected before the regulatory approval, while the trial is on-going, when subjects are currently being enrolled in a trial/research or completed on a routine basis or sometimes when triggers by a complaint or there is a suspicion of serious non-compliance integrity issues and/or scientific/ethical misconduct.

Generally, GCP inspections are announced. However unannounced inspections may also be possible.

11. TYPES OF GCP INSPECTIONS:

The GCP Inspections can either be routine, triggered, or can be conducted in response to anapplication.

11.1. Routine GCP inspections:

Routine inspections are inspections carried out as a routine surveillance of GCP compliance in the absence of specific trigger elements. These inspections are announced and can be conducted before, during or after completion of Clinical Trial/Research. The duration of the inspection and the number of inspectors present on an inspection will vary depending on the complexity of the Clinical Trial/Research and activities conducted at the site/center and it shall be decided by the CSC.

11.2. Triggered GCP inspections:

This is an inspection requested/directed by the CSC where there is a concern due to either the actual issues observed or the potential impact of deviations from GCP on the conduct of the study as a whole or at a particular site or when a serious violation or breach of GCP standards has occurred. This type of inspection may be done announced or unannounced and applies to ongoing or completed clinical trials/research and decided by the CSC.

12. GCP INSPECTION PROCESS:

The complete process for conduct and reporting of GCP Inspection is described below:

12.1. Nomination/Notification of GCP Inspection Team:

GCP inspectors nominated by the CSC and/or notified by the Authority shall perform the inspection. A member of the CSC or any other expert nominated by the CSC or the Chairman CSC, may accompany the inspection team as an expert. The inspection team will be constituted considering on the phase or type of trial/research, intervention / the investigational medicinal product, and other variables considered relevant on a case by case basis by the CSC. The inspectors should be well qualified and have valid GCP qualification/certification.

DRAFT FOR COMMENTS

The team will have a lead inspector responsible for coordinating the inspection, collating the information from team members, and finalizing the inspection report.

12.2. Notification of schedule of GCP Inspection:

In general, the Investigator, Sponsor, CROs, Site/Center or Bio-Analytical Laboratory of a Clinical Trial/Research will be notified at least 7-10 days prior to the proposed announced inspection date and asked to confirm availability of inspectee and relevant personnel. The notification of schedule will identify the study, the proposed sites to be inspected and, the proposed date(s) of inspection. In relation to triggered inspections, the CSC/DRAP may provide a shorter notice period or may conduct unannounced/surprise inspection.

The following information may be requested from the inspectee (Investigator, Sponsor, CROs, Site/Center or Bio-Analytical Laboratory of a Clinical Trial/Research) to be submitted to the CSC/DRAP;

- Research participant/enrolment status per trial site (number randomized, drop-out rate, and number ofserious adverse events reported per site), at trial initiation or during the trial.
- Copies of study standard operating procedures along with amendments e.g. (monitoring procedure, informed consent procedure, serious adverse event reporting procedure, IMPs / drug supply procedure).
- Trial-specific document such as Trial Master File (TMF) or Investigator Site File (ISF), a copy of the current protocol and protocol amendment and informed consent form, source data verification guidelines, IMPs/product handling instructions, laboratory manual, randomization code (if it is necessary), breaking procedure (if it is necessary), monitoring plans and reports.
- Updated CV of principal investigator or investigators, and members of the IRB.
- Arrangements for direct access to any computerized systems upon which trial date or essential documents are stored.
- Any other documentation deemed necessary by the inspectors.

An inspection plan, outlining the sites to be inspected and the schedule of meetings to be held with the Investigator(s) and/or Sponsor will be provided prior to the inspection to the inspectee. The Trial Master File comprising the essential documents which will enable both the conduct of the trial/research and the quality of the data produced, to be evaluated must be available by direct access and shall provide the basis for the GCP inspection.

12.3. Pre – inspection preparation

The inspection schedule/dates will be confirmed with the inspectee (incase of announced GCP inspections only) and the inspectee may be required to submit the aforementioned data/documents to the CSC / Pharmacy Services Division-DRAP on priority but not later than 14 days of the receipt of the notice of GCP inspection, along with relevant essential documents. The inspection plan shall be finalized by the nominated panel coordinator.

Each team member should become familiar with all the relevant documents, including the Study Protocol(s), Informed Consent Forms, Clinical Trial Report(s), Case Report Forms, Adverse Event Reports, Research Study / Site information, and other related documentation.

12.4. Conduct of GCP inspection

12.4.1. Opening Meeting:

GCP inspections will start with an opening meeting, document review, interview sessions, visit to site facilities and a closing meeting as indicated in the inspection plan. An opening meeting will be conducted with Principal Investigator and study team/staff by the inspectors, where the inspectors will explain the GCP inspection plan, and also confirm that the resources, essential documents and facilities required for the inspection are available.

12.4.2. Presentation/Overview of Research:

The inspectee/PI/SI shall be required to present a general overview of the Clinical Trial/Research at this meeting, information regarding the recruitment of subjects, informed consent process, investigational product management, safety reporting, biological sample handing etc.

DRAFT FOR COMMENTS

12.4.3. Interview(s) of Study/Research Team:

During inspection, the inspectors may interview Investigator/Study team/staff and participants to determine how the trial/research is conducted and may ask questions relating to study staff, Institutional Review Board (IRB), Investigator Site Files, Trial Participant Recruitment, Informed Consent, Investigational ProductManagement, Safety Reporting, Biological Samples handling, Source Documents, Case Report Forms, record keeping, monitoring, etc.

12.4.4. Visit of Site/Center Facilities:

The GCP Inspectors shall visit facilities used to conduct Clinical Trial/Research activities.

12.4.5. Document Review:

The activities and documents to be examined during the routine type of GCP inspection undertaken by the CSC/DRAP are outlined below;

Protocol specific inspections may include:	System Inspection may include:
• Trial Master File • Legal and administrative aspects • Communication with the ethics Committee • Communication with the National Bio-Ethics Committee • Communication with the CSC/DRAP • Other Communications • Organizational aspects • Implementation of the trial at the investigator site • Facilities and equipment • Management of biological samples • Organization of the documentation • Monitoring and auditing • Use of computerized systems • Informed consent of trial participants • Details of impartial witness if any • Review of the trial participant data • Adverse event reporting • Management of the investigational medicinal product(s) • Protocol deviations • Other, as required by the GCP Inspectors.	○ Organization and personnel ○ Facilities and equipment ○ Sponsor/CRO Operating Procedures ○ Implementation and termination of the clinical trial ○ Monitoring ○ Investigational Medicinal Product ○ Sample management ○ Safety and adverse events reporting ○ Data handling and clinical trial report ○ Documentation archiving ○ Sponsor audit and quality assurance system ○ Management process for protocol deviations ○ Delegation of duties ○ Other, as required by the GCP Inspectors

All the essential documents concerning a clinical trial must be available for inspection. A TMF/ISF for a clinical trial must contain all documents which individually and collectively permit evaluationof the conduct of a trial and the quality of the data produced. The TMF/ ISF must be established from the onset of the trial and kept updated on an ongoing basis as the trial completes different stages. All the essential documents contain a minimum list of documents generated before, during and after the trial, which must be stored in the TMF/ ISF with the Sponsor and Investigator, respectively. If certain documents are assessed not to be of relevance to the TMF/ISF, it must include a reason for omitting these documents in a timely manner.

The inspectee must ensure that a list of source data is available with a description of where source data etc. can be found. Source data may be both electronic and on paper. A list of such data includes medical records, laboratory reports, diaries, dispensing logs, ECG print-outs, Case Report Forms (CRF), X-ray images, radiological reports, etc. The list of source data must be prepared before the trial/research is initiated. It must be signed and dated by the principal investigator or by a person whom theprincipal investigator has delegated or assigned this task. The list must be available in the TMF/ISF.

12.4.6. Closing/Exit Meeting:

At the end of GCP inspection, there will be an exit meeting where the inspectors will present the GCP inspection findings and grading (As defined in the guidelines and inspection Checklist) to the inspectee(s) and ensure that results of the inspection are clearly understood.

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13. REPORTING OF GCP INSPECTION

13.1. Report of GCP Inspection:

Following the GCP-inspection, the inspectors will prepare a report on specified format as given in the instant guidelines (Annexure-I), within 05 days. Inspection panel coordinator will submit GCP inspection report to the Pharmacy Services Division. The within 10-15 days after receipt of the report, . In case of any finding which needs to be resolved at a time or is critical observation and can harm wellbeing of trial participants then inspection panel shall immediately inform to the Chairman CSC for necessary decision in this regard. The written inspection report should be signed by all inspectors in the inspection team after consolidating their inputs. In general, written reports are issued in paper format and(or) an electronic copy is sent to a nominated contact/focal person if requested.

The inspection findings should be classified as critical, major and minor as per definitions described in these guidelines and in the GCP inspection checklist below. The inspection report shall summarize and evaluate the potential implications of any minor, major and/or critical findings described within the inspection report with respect to the impact on the integrity of the trial data, rights, wellbeing and safety of the study participants and the compliance of the trial/research with ICH-GCP Guidelines including ethical principles and the Bio-Study Rules, 2017.

13.2. Corrective Action and Preventive Action Plan

Upon receipt of GCP Inspection report, the Pharmacy Services Division shall assess the report and issues the inspection observations for submission of CAPA within 10-15 days by the PI/Sponsor/inspectee.

13.3. Closure and Final Report of GCP Inspection:

Upon receipt of the responses (CAPA) form PI/inspectee, the Pharmacy Services Division shall review the responses within fifteen (15) days and if required a follow up inspection for CAPA verification may be done.

13.4. Decision and Notification on GCP Inspection:

The final inspection report/findings shall be placed before the CSC for discussion. The CSC may invite the inspectee for a discussion in case of defense or clarifications as needed. Inspectees may appeal before the Authority against the CSC decision as per Rule 23 of the Bio-Study Rules, 2017.

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ANNEXURE-I

GCP INSPECTION CHECKLIST

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A. DESCRIPTION AND GRADING OF GCP INSPECTION FINDING

Critical (CR)	
Definition	• Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrityof data. • Critical observations are considered totally unacceptable.
Possible consequences	• Rejection of data and/or legal action required.
Remark	• Observation classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.
Major (MA)	
Definition	• Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrityof data. • Major observations are serious deficienciesand are direct violations of GCP principles.
Possible consequences	• Data may be rejected and/or legal action required.
Remark	• Observations classified as major, may include a pattern of deviations and/or numerous minor observations.
Minor (MI) / Other	
Definition	• Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data.
Possible consequences	• Observations classified as minor, indicate the need for improvement of conditions, practices and processes.
Remark	• Many minor observations might indicate a bad quality and the sum might be equal to a majorfinding with its consequences.
Comments	• The observations might lead to suggestions on how to improve quality or reduce the potentialfor a deviation to occur in the future.
Responsibility for the finding	• The responsibility for addressing the finding will be stated. This could be Sponsor/CROs, Principal Investigator, IRB/IEC/ERC etc.

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B. GCP INSPECTION CHECKLIST

Names & Designation of GCP-Inspector(s)	• • • • •
Date of GCP-Inspection	
Name and address of the site	
Trial/Research Protocol Number	
Stage/Status of the Study:	
Timing of GCP-Inspection	• Before trial commencement ☐ • During clinical research conduct ☐ • After completion of trial/research ☐ (Tick/encircle one)
Name of Principal Investigator	
Name(s) of Co-Principal Investigator	
Name(s) of Site-Principal Investigator	
Study Title	
DRAP/CSC Approval / Registration No	
Research/Trial Protocol No. Version & date:	
Amendment(s) approval history: Version & date:	
IRB/ERC Protocol approval Version & date:	
NBC Protocol approval Version & date:	
Informed Consent Form Version approved & date:	
ICF Amendment History approval Version & date:	
Screening date of 1st participant	
How many participantsenrolled? (till date of GCP-Inspection)	
How many participantswithdrew from the study?	
How many participantscompleted the study?	

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Observations are classified into the categories "Critical", "Major", "Minor/ Other" as defined in Section-A above. The recommendations are listed at the end of the report.

A. FACILITY INSPECTION	YES	NO	NA	Observation/Grading
1. Consulting Area				
1.0 Does the area for individual participant informed consenting provide the required privacy to maintain confidentiality?				
1.1 Is the consulting area where the PI/designated person evaluates the participants during visits adequate in size?				
1.2 Are there lock-up cupboards for confidential documents?				
1.3 Is the trial specific equipment available in the consulting room?				
1.4 If not, is the area where procedures are performed adequate and easily accessible?				
1.5 Does the PI manage and maintain the trial visits? To add to inspection training that this could be not applicable in the case of field sites				
2. Procedure Room				
2.1 Is all equipment e.g. sphygmomanometer, scale(s), etc. as required per protocol calibrated and validated?				
2.2 Are SOPs on how to use equipment available?				
2.3 Is the phlebotomy/blood sampling area kept according to infection controlprocedures?				
2.4 Waste handling according to applicable guidelines.				
2.5 Is the emergency trolley available in the procedure area? As perthe requirements for vaccines and medical devices. 2.5.1 Does the facility have emergency power back up tomaintain drug temperatures and sample storage? 2.5.2 Is the trolley locked and are the keys available and controlled? 2.5.3 Are expiry dates clearly checked and controlled? 2.5.2 Is the emergency trolley frequently checked and documentation as proof available? 2.5.4 Oxygen and accessories available, checked andsigned? 2.5.5 Are PI and sub-investigators ALSS trained? 2.6. Are clinical staff CPR trained?				
3. Pharmacy (Investigational Product Storage Area)				
3.1 Is the pharmacy access controlled, temperature and humiditycontrolled?				
3.2 Are vaccines stored as per required temperature and humidity?				
3.3 Is the preparation of investigational product management done according to the approved protocol by suitable qualified staff?				
3.4 In case of vaccines, are a spillage SOP available and the studyteam trained to handle such an incidence?				
3.5 Are electronic or hand-written temperature logs available?				

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3. Pharmacy (Investigational Product storage area)	YES	NO	NA	Observation/Grading
3.6 Is an SOP on how to handle electricity or temperature failure in the pharmacy available?				
3.7 Are the different studies Investigational Products kept in separate lock-up cupboards and clearly identified'?				
3.8 Are vaccines transported and handled as per cold chain requirements?				
3.9 Have any temperature deviation occurred? If yes, what was the temperature recorded and estimated duration of exposure?				
4 Archive				
4.1 Is there an agreement between Sponsor and Trial Site / CRO on the archiving of documentation?				
4.2 Is this clause documented in the protocol or contract				
5 Clinical Laboratory				
5.1 Is the clinical laboratory at the same site?				
5.2 If not, are procedures in handling biological samples clearly documented?				
5.3 Are all equipment and testing procedures used in the laboratory validated?				
5.4 Is the laboratory accredited for the tests to be performed?				
6 Waste disposals				
6.1 Is the disposal of biological specimens and sharps appropriate?				

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B. DOCUMENTATION

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor and Monitor with the standards of GCP and all applicable regulatory requirements. **(ICH GCP Section 8)**

Check the *availability* of the following documents:

(During the planning stage, the following documents should begenerated ***before*** the conduct of the trial) **General**	**YES**	**NO**	**NA**
1.1 Approved, signed and final version of the Protocol (includingamendments)			
1.2 Final version of the Investigator's Brochure			
1.3 Information Leaflet, information regarding the trial in lay terms			
1.4 Informed Consent Form (translation) and applicable procedure			
1.5 Sample of the case report forms (CRF) as per protocolrequirements			
1.6 Any other written information (e.g. advertisements)			
1.7 IRB / IEC approval			
1.8 Financial aspects of the trial as predefined in an agreement between the Investigator and the sponsor			
1.9 Guaranteed indemnity / insurance document / statement			
1.10 Signed agreements between involved parties e.g. Investigator / CRO, Investigator/Sponsor			
1.11 Source documents and CRF verification procedure (SOPs) available?			
1.12 Clear documentation of transfer of responsibilities			
1.13 All approval documentation:			
(During the planning stage, the following documents should be generated ***before*** the conduct of the trial) **General**	**YES**	**NO**	**NA**
• Independent Ethics Committee approval (Clearly stated which dated version of protocol and informed consent is approved.) • Regulatory approval. (Clearly stated which dated version ofprotocol and informed consent is approved.)			
1.14 List of Ethics Committee members			
1.15 Latest signed and dated CV's of investigators			
1.16 Proof of GCP training of all study team members			
1.17 Pre-trial GCP site assessment report (only at the Sponsor site)			
1.18 List of DSMB members (if any)			
1.19 Verify the availability of the Local Safety Monitor's CV			
1.20 Trial initiation visit, agenda and study team attendance list			
1.21 Verify the availability of the Serious Adverse Event reporting forms and reporting procedures/timelines (including supporting SOP's)			
Laboratory			
1.22 Normal values / ranges for medical / laboratory / technicalprocedures as supplied by the laboratory / contract laboratory			
1.23 Laboratory Certification			
1.24 Laboratory Accreditation			
1.25 Quality Control or quality assessment of laboratory by thesponsor			
1.26 Validation methods where applicable			
Investigational Product			
1.27 Sample labels of IMPs			
1.28 All shipping records of IMPs (dates, batch numbers, Dru Import License & Clearance certificate etc.)			
1.29 Proof that conditions as stated in the protocol have been maintained during			

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shipment and storage of products			
1.30 CoA of IMPs (Check stability, expiry dates)			
1.31 Vaccine / IMPs accountability records e.g. quantities ordered and received			
1.32 Decoding procedures for blinded trials			
(During the planning stage, the following documents should begenerated ***before*** the conduct of the trial) **General**	**YES**	**NO**	**NA**
1.33 Master randomization list availability			
1.34 Instruction for handling of investigational product and trial related materials			
1.35 Proof that the correct diluent has been packed according to thecorrect storage condition and shipped with the vaccine?			
2 ICH GCP section 8.3 (In addition to having on file the aforementioned documents the following documentation should be added to the files ***during*** theconduct of the trial) **Documentation**	**YES**	**NO**	**NA**
2.1 Updates of Investigator's Brochure e.g. ADRs			
2.2 Any approved amendments to o protocol o informed consent forms and/or o any other trial documents			
2.3 IRB/IEC and regulatory approval of any new investigators, and theirCVs			
2.4 Proof of GCP training			
2.5 Updates of normal values / ranges for medical / laboratory / technical procedures as supplied by the laboratory / contract laboratory			
2.6 IMPs accountability documentation and correct use of theproduct according to the protocol and IMPs management			
2.7 Shipment documentation of any new batches of IMPs includingCoA, batch release and temperature control.			
2.8 Communications other than monitoring visits o Letters o Meeting minutes and agendas o Notes of telephone calls			
2.9 Signed Informed Consents			
2.10 Source documents, e.g. X-rays, serology printout, diary cards etc.			
2.11 Signed and dated CRFs			
2.12 SAE reporting to Sponsor			
2.13 Reporting of any serious unexpected ADR and relevant safetyinformation to DRAP, NBC and IRB where required			
2 ICH GCP section 8.3 (In addition to having on file the aforementioned documents the following documentation should be added to the files ***during*** theconduct of the trial) **Documentation**	**YES**	**NO**	**NA**
2.14 Progress reports to IRB/IEC			
2.15 Participant screening log			
2.16 Participant identification code list			
2.17 Participant enrolment log			
2.18 Study team signature sheet with delegated functions by PI			
2.19 Retained biological samples (records, storage conditions)			
2.20 All deviations e.g. inclusive/exclusive criteria (waiver)recorded			
3 ICH GCP section 8.4 (Documentation ***after*** completion or termination of the trial)			

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3.1	IMP accountability at site(s) (final reconciliation)			
3.2	Documentation on disposal of IMPs			
3.3	Completed participant identification code list			
3.4	Audit Certificate (if applicable), i.e. if carried out			
3.5	Final trial close-out monitoring report			
3.6	Final report by investigator to IRB/IEC, NBC and the DRAP (refer to ICH GCP section 4.13)			
3.7	Clinical Study Report (refer to ICH GCP section 5.22)			
3.8	Treatment allocation and decoding documentation that have occurred available.			
3.9	Is a follow up plan available (post trial period) for participantswith adverse events related to the IMP as per protocol?			

C.	**INFORMED CONSENT PROCESS**	**YES**	**NO**	**NA**
1	Was the informed consent form version used the same as the oneapproved by the IEC/IRB?			
2	Was a written SOP used to solicit informed consent?			
3	Were all the participants given a copy of a signed informedconsent form?			
4	Did all the participants sign the consent form prior to any studyrelated procedure?			

D. GENERAL INFORMATION

1 Ask for an organogram of the Trial Site/CRO and note the following points:
- 1.1 Number and categories of people employed;
- 1.2 Description of the qualifications, training and experience of the personnel;
- 1.3 Work load of study team;
- 1.4 Number of concurrent clinical studies performed on site and identification of participants to avoid confusion and mix-ups of IMP's administration.

2 Ask for a description of the quality assurance system set up at the trial site.

3 Check the existence, availability, accessibility and validity of the operating procedures; ask for a list of the Standard Operating Procedures used for the trial.

4 Verify the availability of 100% of all documentation particularly the ICF, CRF and source documents.

5 Perform verification of Informed Consent forms as per DRAP requirements.

6 Perform at least 25% Source documentation versus CRFs verification

7 Perform a100% accountability of IMPs

E. Any other Information / Detail as required by panel or provided by inspectee.

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DRUG REGULATORY AUTHORITY OF PAKISTAN
Pharmacy Services Division, DRAP-NCLB Building,
Prime Minister's Health Complex, Park Road,
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